

Treatment of Severe Burns using Stem Cell Therapy

Jessica Stepp¹ and Vincent S. Gallicchio^{2*}

¹Department of Biological Sciences, College of Science, Clemson University, Clemson, SC 29627

²Department of Biological Sciences, 122 Long Hall, College of Science, Clemson University, Clemson, SC 29627

***Corresponding author:** Vincent S. Gallicchio, Department of Biological Sciences, 122 Long Hall, College of Science, Clemson University, Clemson, SC 29627

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Abstract

Severe burn injuries pose a major clinical threat due to extensive damage to the integumentary system and subsequent systemic disturbances that require advanced medical intervention and long-term rehabilitation. In this review, severe burns are defined as second- and third-degree burns covering substantial body surface area (20% in adults, 10% in children or elderly). Modern medical interventions have proven to be successful in lowering morbidity and mortality rates among these victims with the recent integrated practices focusing on preliminary treatment to prevent burn shock and burn wound sepsis. However, treatments focusing on tissue regeneration and regain of function remain insufficiently researched. Stem cell-based therapies have recently emerged as a promising approach to accelerate wound healing, enhance reepithelialization, and restore dermal structures. Current data suggests epithelial stem cells (EpSCs) and mesenchymal stem cells (MSCs) have shown the greatest potential in preclinical and early clinical regenerative studies. This literature-based review evaluates current evidence regarding the safety, efficacy, and therapeutic mechanisms of EpSC and MSC treatment in severe burn wounds. Additionally, it assesses the consensus data on cell dosage, delivery protocols, experimental outcomes, and remaining challenges regarding stem cell treatment in severe burns and chronic wound healing.

Keywords

Severe burn; Stem cell therapy; Modern medical; Cell dosage; Burn modalities.

Abbreviations

- Acute kidney injury- AKI
- Acute respiratory distress syndrome- ARDS
- Adipose-derived mesenchymal stem cell- ASC
- Blood brain barrier- BBB
- Bone marrow derived-mesenchymal stem cell- BM-MSC
- Burn-derived mesenchymal stem cell- BD-MSC
- Cultured epithelial autografts- CEA
- Dermal stem cell- DSC
- Eccrine sweat gland stem cell- SGSC
- Epidermal stem cell- ESC
- Epithelial stem cell- EpSC
- Epithelial stem cell-derived exosome- EpSC-Exo
- Gastrointestinal- GI
- Hair follicle-derived mesenchymal stem cell- HF-MSC
- Interferon gamma- INF- γ
- Interleukin-1- IL-1
- Mesenchymal stem cell- MSC
- Multi-organ dysfunction syndrome- MODS
- Negative pressure wound therapy- NPWT
- Platelet-derived growth factor- PDGF
- Stromal vascular fraction- SVF
- Systemic inflammatory response syndrome- SIRS
- Transforming growth factor- β - TGF- β
- Transforming growth factor- β 1- TGF- β 1
- Transient amplifying- TA
- Tumor necrosis factor alpha- TNF- α
- Umbilical cord-derived mesenchymal stem cell- UC-MSC
- Umbilical cord-derived mesenchymal stem cell-derived exosome- UC-MSC-Exo
- Vascular endothelial growth factor- VEGF

Introduction

Background on burns

Burns are classified as tissue damage that occurs from extreme or prolonged exposure to heat, electricity, radiation, chemicals, or friction. The skin is made of three layers; the epidermis, dermis, and hypodermis (subcutaneous tissue). The epidermis is the outermost layer, which provides organisms with a protective barrier to the external environment. The epidermis is arranged in strata, or layers, consisting of keratinocytes, melanocytes, Langerhans cells, and Merkel cells. The dermis is located under the epidermis; this layer contributes 90% of the thickness of an organism's skin. The epidermis gets its bulkiness from a

vast network of both loose and thick connective tissue, collagen and elastic fibers. The epidermis also houses sweat glands and sebaceous glands, nerve endings, blood vessels, and hair follicles making it a key player in maintaining organismal homeostasis. The deepest tissue layer of the skin is the hypodermis or subcutaneous layer. It is primarily composed of adipose tissue and areolar connective tissue, as well as some blood vessels, nerves, and collagen fibers. The tissues of the hypodermis provide insulation and protection for the internal environment, as well as serve as attachment sites to the underlying muscles and bones [1,2]. The three layers of the skin work together to encapsulate the internal organism and protect it from harm.

In 1947, Douglas Jackson described the three zones of burn injuries as follows; the zone of coagulation occurs at the point of maximum damage and results in irreversible tissue loss due to coagulation of the constituent proteins. The zone of stasis, which surrounds the zone of coagulation, and is characterized by decreased tissue perfusion predominately leading to apoptosis and tissue loss. The tissue in this zone is potentially salvageable if revascularization is achieved within a few days [3]. Burn resuscitation aims to increase tissue perfusion in this region and prevent any damage from becoming irreversible. However, if prolonged hypotension occurs, infection or oedema, this area experiences complete tissue loss. Lastly, the outermost zone known as the zone of hyperemia is where tissue perfusion is increased as a physiological response to the burn. The tissue here will recover unless there is severe sepsis or prolonged hypoperfusion.

The severity of burn depends on the size and depth of the injured tissue (Figure. 1) [4]. First-degree burns, also known as superficial burns, only affect the outer layer of skin (epidermis). These burns are characterized by redness and pain, with no blister formation. In epidermal burns, healing time is between 3–7 days and normal function is regained. Second-degree (partial thickness) burns affect the epidermis and bleed into the deeper tissues of the dermis. Second-degree burns appear red, painful and inflamed with blisters. Burns that affect only the upper layer of the dermis (papillary layer) take 1–3 weeks to heal and leave the victim with long term pigment changes but minimal scarring. Deeper burns affecting both the papillary layer and the lower reticular dermis take 3-6 weeks to heal, and scars are formed. The most severe type of burns is third-degree, or full thickness, burns. These completely destroy both the epidermis and dermis tissue, with the possibility of damaging the underlying bone and muscle. Third-degree burns appear white or charred. Patients with third-degree burns lose all sensation due to nerve endings being destroyed. Full thickness burns that spread to the subcutaneous tissue or deeper do not heal without skin graft assistance [3,5]. Severe burn injuries directly affect the integumentary system but can cause downstream trauma to multiple other body systems, often leaving those inflicted with systemic complications.

Importantly, children with burns affecting just 10% of their total body surface area (TBSA) and adults with burns covering 15–20% are considered critically injured and require hospitalization and long-term rehabilitation. Burn wounds are also particularly complex to treat and manage in vulnerable groups such as children under 5 and adults over 60 [5-7]. This is due to the physiological limitations as well as increase in risk of complications that often constrain healing in the young and elderly. Severe burn injuries not only devastate the integumentary system but also trigger systemic complications affecting multiple organ

systems.

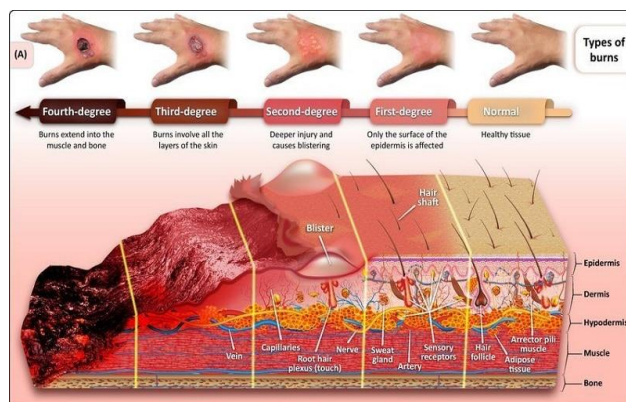


Figure 1: Degree of burns shown by hand models and a cross section of the integument.

Burn modalities

Thermal burns can be scalds occurring from a hot liquid, flame burns occurring from hot gas, or contact burns occurring from a hot object. Scalds result in 70% of burns seen in children. Common mechanisms are spilling hot liquids or being exposed to too hot of bath water. These burns cause superficial to superficial dermal burns. Flame burns are seen in 50% of burns in adults. Often associated with inhalation injury and other concomitant trauma. Flame burns tend to be deep, dermal or full thickness. Contact burns are common in people with epilepsy or those who use alcohol or drugs and occur when a hot object is touched or held onto for too long. These tend to be deep dermal or full thickness.

Electrical burns occur when an electric current runs through the body and damages tissue in its path. The amount of heat generated determines the level of tissue damage and is equal to how high the voltage is. High voltage injuries are split between two categories; true high tension burns which are caused by voltage passing through the body and flash burns which are tangential exposure to a high voltage current where no current penetrates the body. Statistically, 3–4% of burn unit admissions are caused by electrocution injuries. Domestic electricity (low voltage) burns are small, deep contact burns. These can interfere with the cardiac cycle giving rise to arrhythmias. True high-tension burns occur when the voltage is 1000V or more. These burns result in extensive tissue damage and often limb loss, usually accompanied with a large amount of soft and bony tissue necrosis. True high tension burns often require more aggressive resuscitation and debridement than other burns. Flash burns occur when there has been an arc of current from a high-tension voltage source, no current passes through the victim's body. This can cause superficial flash burns to exposed body parts. Clothing can also be caught on fire giving rise to deeper burns.

Chemical burns tend to be deep due to corrosive agents; these agents can cause coagulative necrosis until completely removed. Alkalis tend to penetrate deeper and cause worse burns than acids. Cement is a common cause of alkali burns. These burns need to be irrigated to limit the depth of the burn and then neutralized to stop the burn from progressing [3,8].

Burn healing

Each layer of the skin facilitates a different mechanism of repair when injured. When undergoing the healing process in the epidermis, the EpSCs will migrate to the site of injury, proliferate, and then further differentiate into keratinocytes to soon re-establish the skin barrier. Deep, dermal burns however, heal much slower, relying heavily on keratinocytes migrating in from surrounding uninjured tissue. This same process explains how the interstices of meshed split-thickness grafts are eventually filled in with keratinocytes moving across the skin bridges. Unlike the epidermis, when dermal tissue is burned it repairs damage through scar formation (Figure. 2) [9]. The alteration in healing mechanism used by dermal tissue is due to the loss of both epidermal and dermal regenerative elements that are vital in healing such as EpSCs and MSCs located in the sweat glands and hair follicles of the dermis [3,10]. The scarring process is characterized by affected tissues being replaced by connective tissue (via collagen production by fibroblasts) which ultimately leads to scar formation. Scar tissue is distinct from regular epithelial tissue, it is composed of a disorganized, rope-like arrangement of collagen fibers rather than an organized mesh of collagen and elastin fibers. Scar tissue also lacks hair follicles, glands, and nerve endings leading to loss of normal function at the area [11]. If healing of the dermis is fully impaired due to extensive tissue loss, fibroblasts responsible for collagen reproduction in the hypodermis can migrate to the dermis and assist in repairing wounded tissue.

All severity of burns follows three basic healing phases; inflammation, proliferation, and remodeling, but are modified based on level of damage, locally and systemically. During the acute inflammatory phase of severe burns, SIRS activation as well as localized inflammation begins. The localized inflammation response is crucial for initial debridement and the initiation of healing. New developments in burn wound pathophysiology indicate that the acute inflammatory response may have negative side effects to patients due to capillary leakage, the propagation of inhalation injury and the increased likelihood to develop multiple organ failure. However, inflammation remains crucial for later stage burn healing [3]. The proliferative phase follows and is characterized by cytokine and growth factors activating keratinocytes and fibroblasts, granulation tissue formation in the dermis, blood vessels begin to grow into the wound-promoting healing and tissue perfusion, and lastly, keratinocyte migration to wound surface. In less severe burns, the proliferative phase results in a closed wound. However, in some second-degree and all third-degree burns, surgical interventions such as skin grafting are needed to complete this phase [12]. The third and final phase, the remodeling phase, involves collagen and elastin restoring the structural integrity of the integument and scar formation. In severe burns, type III collagen is initially placed during the proliferative phase and replaced during the remodeling phase by type I collagen, which results in hypertrophic scarring and stiffness [13].

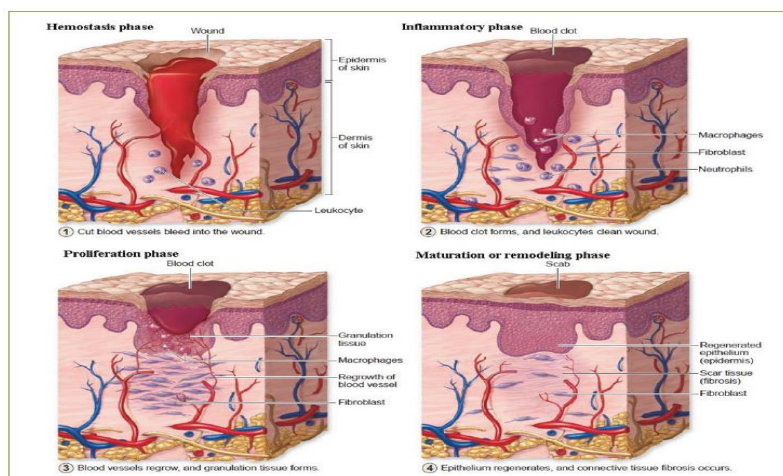


Figure 2: The stages of burn wound healing in the dermis and epidermis.

As the body's largest organ, trauma such as burns to the skin can drastically endanger an organism's health and wellbeing. Toxic metabolites, cytokines and other inflammatory mediators at the site of injury have a systemic effect once the burn reaches 30% of total body surface area— this is known as burn shock. Locally, mediators such as histamine, serotonin, bradykinin, nitric oxide, free radicals, and eicosanoid products (prostaglandins, thromboxane), along with cytokines like TNF and interleukins are released. Histamine in particular is considered a key factor in early increase of vascular permeability, causing endothelial cells in venules to contract and form transient gaps. This allows for plasma leakage and contributes to the rapid development of edema in severe burn victims. Experimental studies suggest that the pathogenesis of burn edema is closely tied to interactions between histamine, xanthine oxidase, and oxygen-derived free radicals [3].

Cytokines and inflammatory mediators released at the burn site also drive systemic changes across multiple organ systems. These include cardiovascular changes- capillary permeability increases leading to loss of intravascular proteins and fluids into the intestinal compartment. Peripheral and splanchnic vasoconstriction occurs. Myocardial contractility is decreased, possibly due to the release of tumor necrosis factor- α (TNF- α). This, plus fluid loss from the wound result in systemic hypotension and organ hypoperfusion. Respiratory changes- inflammatory mediators cause bronchoconstriction, and in severe burns adult respiratory distress. Metabolic changes- basal metabolic rate increases up to 3 times. This, coupled with splanchnic hypoperfusion require extra nutrients to decrease catabolism and maintain gut integrity. Immunological changes- non-specific down regulation of the immune response occurs, affecting both cell mediated and humoral pathways [14].

Once a severe burn occurs, multiple organ systems begin deploying healing mechanisms. The immune system triggers systemic inflammatory response syndrome (SIRS). This response activates widespread defense mechanisms throughout the body, which can lead to multiple organ dysfunction or failure. The body initiates wound healing via activation of inflammatory cells, fibroblasts, and keratinocytes. Their activity is regulated by a complex system of multiple cytokines and host neuroendocrine mechanisms. Principal molecular regulators of this process include vascular endothelial growth factor (VEGF), platelet-

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derived growth factor (PDGF) and transforming growth factor- β (TGF- β). TGF- β is an essential component of the activation and proliferation of fibroblasts during the initial stages of wound healing. Without TGF- β hypertrophic scars, disfigurement and deformity occur [3].

The cardiovascular system is affected due to massive fluid loss and inflammation. The cardiovascular system has two phases. The initial “Ebb” phase which is characterized by increased capillary permeability and a flooding of plasma to surrounding tissue, leading to hypovolemia and a drop in cardiac output. The latter phase, or hyperdynamic “Flow” phase exhibits elevated stress hormones that increase heart rate, cardiac output, and blood pressure in an effort to compensate for fluid loss. The Flow phase puts increased stress on the heart which can lead to eventual cardiac dysfunction [15].

The immune system triggers massive, systemic inflammatory responses that lead to hyperinflammation and immunosuppression. The body is flooded with pro-inflammatory cytokines such as TNF- α and interferon gamma (INF- γ) to clear damaged tissue and fight potential infection. At the same time, anti-inflammatory pathways are activated which suppress the immune system leaving the patient extremely vulnerable to infection and sepsis [16].

The endocrine and metabolic systems are both increased and held in a prolonged heightened state. The elevated endocrine system leads to hyperglycemia and insulin resistance. The elevated metabolic rate is caused by the release of stress hormones; long term it promotes breakdown of proteins and fat to be used as fuel [17].

The nervous system initiates a systemic stress response resulting in peripheral and central sensitization as well as blood brain barrier (BBB) breakdown. Sensitization is a result of nerve endings at the burn site sending constant, intense pain signals which results in chronic neuropathic pain, hypersensitivity, and itchiness. The BBB breakdown is caused by inflammatory molecules entering the brain because of the widespread inflammation. The inflammatory molecules cause neuroinflammation and can lead to long-term cognitive issues such as memory loss [18].

Acute kidney injury (AKI) is a common complication that is inflicted on the renal system from severe burns. Kidney tissue can die due to the systemic hypovolemia and hypoperfusion. The catabolism of muscle tissue (seen predominately in severe electrical burns) releases myoglobin, which damages the kidney tubules [19].

Lastly, if the pulmonary system is injured, inflammation and swelling can lead to airway edema. Additionally, the systemic inflammatory response can result in fluid buildup in the lungs, impairing gas exchange and increasing the potential of acute respiratory distress syndrome (ARDS) developing [20].

Systemic complications due to severe burns often have a rapid onset and can be life-threatening. Over 60% of burn-related deaths are due to sepsis, septic shock, and multi-organ dysfunction syndrome (MODS). Data shows mortality rates were highest in those with inhalation injury (77%) and early SIRS (79%). Furthermore, infection and inhalation injury accounted for 40% and 33% of mortality, respectively. Gastrointestinal (GI) dysfunction was also present in 88% of deceased burn victims [21].

Current burn treatment

Through medical advancements, treatment for severe burn victims has increased in knowledge and sophistication leading to lower morbidity and mortality rates. Clinical management of burn injuries incorporates multiple approaches aimed to minimize damage, promote wound closure, and prevent complications. In the pre-hospital setting, immediate topical cooling with room-temperature water (15°C) has been shown to maximize epithelialization and reduce future scarring, providing equally effective results as cool water (2°C) and superior to ice water [3]. Other essential components of early burn care include fluid resuscitation, infection control, nutritional support, and management of the hypermetabolic response. Among the most significant advancements in recent decades has been the adoption of early surgical intervention. Aggressive approaches such as early tangential excision and sufficient wound closure have been associated with improved mortality rates. In patients with burns over 20% TBSA the mortality rate was significantly decreased with excision done within the first three days (3.8%) compared to 8-14 days (6.1%) [22]. By excising the wounded tissue early on, clinicians are able to reduce the local and systemic inflammatory effects of mediators released from burned tissue [3]. This practice limits progressive pathophysiologic events such as infection and sepsis that would likely occur otherwise.

Despite vast improvements, significant challenges persist in treating patients with extensive burns due to the lack of sufficient uninjured skin available to be grafted for treatment. Current clinical practices for wound coverage in burn victims include autologous skin grafting, the use of skin substitutes, and negative pressure wound therapy (NPWT). Patients with sufficient amounts of viable skin are often treated with autologous skin grafts to promote reepithelization in lost tissues. However, when a patient has limited surface area of uninjured skin, adequate amounts of skin grafts cannot be acquired. Biological substitutes such as amnion and cultured epithelial autografts (CEA) have been successfully used but carry high risks of contamination and require long-term care. Synthetic substitutes such as Biobrane® and Suprathel® have shown favorable results in promoting healing and reducing pain but are associated with hypertrophic scarring and high infection risk [19]. Additional advanced treatment approaches involve biomaterials such as silk fibroin, metal-doped calcium silicate, and polymeric hydrogen scaffolds. These treatments focus on reepithelization, promoting angiogenesis, reducing infection risk, and improving biocompatibility [23].

Novel burn treatments focus on increasing wound healing efficacy and decreasing infection and rejection risk. These treatments include regenerative approaches such as stem cell therapy and autologous cell suspensions (such as RECELL), as well as advanced tissue engineering through 3D bioprinting and nanotherapeutics. Regenerative approaches are highly anticipated to shape new treatment methods for severe and chronic wound management. Stem cell therapy shows promising preclinical results. Studies suggest they hold the potential to overcome immunological issues associated with burns, improve wound healing, and provide more effective skin coverage for severe burn patients. RECELL or “spray-on-skin” is another regenerative method being researched which consists of an autologous cell suspension that is sprayed onto the injured area, promoting the formation of new skin cells. This treatment option has proven effective when used in conjunction with mesh split-thickness skin grafting, but when used alone resulted in hypertrophic scars [24]. No universally effective wound coverage treatment currently exists; available substitutes are often ineffective, immunogenic, slow to produce in adequate quantities, or highly costly [25]. These limitations have directed increased attention toward regenerative medicine, and more

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specifically, stem cell research.

Stem cells

Stem cells are defined by their unique self-renewal and differentiation capabilities. These undifferentiated cells can divide to produce identical stem cells while simultaneously giving rise to progenitor cells with distinct, specialized functions [1]. This dual ability makes them crucial for tissue maintenance, repair, and regeneration. In the context of possible treatment facilitating wound healing, their qualities make them a desirable candidate for testing. More specifically, skin-associated stem cell lineages such as MSCs of the dermis and EpSCs of the epidermis are theorized to play a major role in leading advancements in burn treatment.

Regeneration itself is a complex process which involves multiple intertwined mechanisms, including inflammation, proliferation, and tissue remodeling. Stem cells have their place in each of these phases, not only through their capacity to differentiate and self-renew, but also through immunomodulatory properties and paracrine signaling. Certain stem cells release cytokines and generate exosomes that contribute significantly to overall wound healing. These factors have been proven to enhance angiogenesis, modulate inflammation, and facilitate the restoration of damaged tissues [1]. By utilizing this, stem cells hold the potential to be powerful agents in regenerative therapy for acute and chronic wounds.

For patients with severe burns, stem cell therapies offer several potential therapeutic advantages including accelerated wound healing, replacement of damaged tissue, and re-establishing epithelial components such as hair follicles, blood vessels, glands, etc. that would otherwise be lost. Importantly, the benefits of stem cell treatment extend past the integument. Stem cells also hold the ability of influencing systemic effects such as mediating inflammation (SIRS), attenuating hypermetabolic responses, and reducing immunosuppression— all of which are crucial for management of extensive burn trauma [11].

Current research highlights gaps in understanding dermal reconstruction during skin healing, but evidence suggests that fibroblast-like cells derived from surrounding tissues as well as mesenchymal progenitor cells and myeloid lineage cells contribute to dermal regeneration. When tissue is burned, these cells migrate to the site of injury and form granulation tissue, which provides the natural scaffold necessary for epithelization and vascularization [25].

In the context of the integument, stem cells reside in the epidermis, dermis and hair follicles, however; the dermis is a larger adult stem cell reservoir compared to both the epidermis and hair follicles. Given that the dominant phenotype in the dermal environment is mesenchymal, mesenchymal stem cells (MSCs) are anticipated to be advantageous in treatment of complex and chronic wounds. MSCs are present in multiple areas of the body, however the dermis houses a specialized type of MSC known as dermal stem cells (DSCs) [25-28]. DSCs can regenerate dermal tissue through their multipotent differentiation capacity to produce melanocytes, fibroblasts, and potentially adipocytes and osteoblasts (Figure. 3) [27]. Research suggests that DSCs are considered to be an accessible and abundant source of

stem cells for therapeutic treatments, as they show great plasticity and potential to differentiate into cells of ectodermal, mesenchymal, and endodermal lineages [29,30]. Epithelial stem cells (EpSCs) are the primary cell type responsible for epidermal repair and are essential for reepithelialization post-injury. These cells reside in niches within the basal layer of the epidermis, the bulge of hair follicles in the dermis, and at the base of sebaceous glands in the dermis. Once activated by a bodily stress response, EpSCs migrate to the wound site and begin to form a new epithelial layer to re-establish the skin barrier. This is accomplished when EpSCs undergo proliferation and differentiation to epithelialize the damaged area [31,32]. In therapeutic capacity, EpSCs have the potential to improve and accelerate healing of burn-injured skin. All three stem cell types are considered to be high potential stem cell lineages for regenerative treatment.

Among the various stem cell sources currently being investigated, dermal hair follicles have emerged as a highly promising and accessible, and most importantly ethically sustainable source of multipotent cells. The MSCs acquired from these are distinct from EpSCs found in hair follicle bulges, with some evidence suggesting they may originate from the neural crest cells rather than the broader ectoderm. Many researchers consider hair follicle-derived MSCs (HF-MSCs) to be one of the most viable and scalable sources of multipotent stem cells for future regenerative therapies for burn victims [11,32].

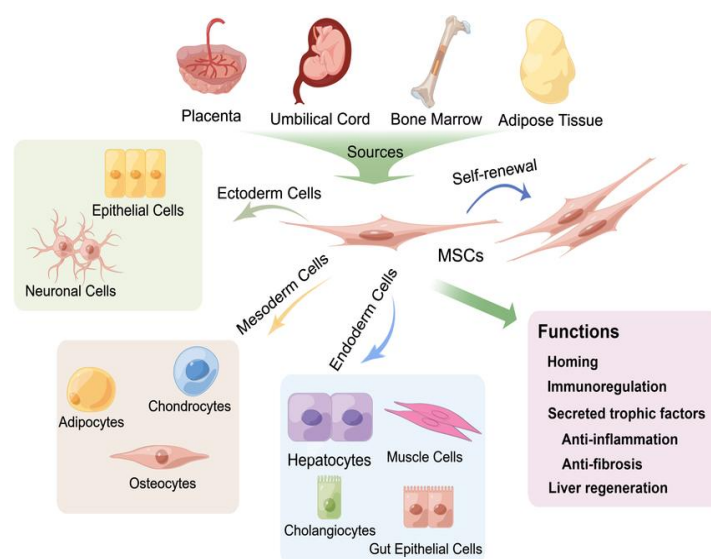


Figure 3: Mesenchymal stem cell differentiation pathways.

Stem cell therapy for burns

Research into stem cell utilization for burn victims remains in its early stages, with experimental studies only beginning to emerge around 2010. Since then, preclinical investigations have consistently demonstrated that incorporating stem cells into burn wound models enhances healing outcomes. The inclusion of MSCs has been shown to accelerate granulation tissue formation, improve collagen deposition, accelerate healing, and enhance overall wound appearance. Additionally, MSC therapy has reduced scarring, supported the regeneration of integument components like hair follicles and sweat glands, and contributed to better regulation of inflammatory markers. Notably, MSCs have also been

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linked to improved vascularization and restoration of dermal thickness and structure post-healing, suggesting that they have significant impact in both dermal and epidermal repair [6]. Alongside MSCs, EpSCs facilitate skin regeneration as they are directly responsible for reepithelialization and restoration of the skin barrier following injury making them a suitable candidate for investigation. EpSC transplantation has the potential to accelerate wound closure and improve the quality of regenerated skin by promoting the formation of organized epidermal layers. Independently, EpSCs and MSCs possess valuable capabilities for highly effective severe burn treatment but combined they could provide a more comprehensive approach to burn recovery.

MSCs in current studies are most often harvested from adipose tissue, bone marrow, and the umbilical cord. Despite their promising nature, none of these sources have yet achieved widespread clinical application due to certain limitations. Bone marrow extraction is invasive and yields limited cells, adipose-derived cells may vary in potency, and umbilical cord cells face logistical and ethical constraints. Furthermore, the risk of immunologic rejection in allogeneic stem cell transplants remains a barrier to advancement of MSC treatment. Another challenge lies in the heterogeneity of fibroblast-like cells involved in dermal repair, raising the possibility that skin-derived mesenchymal cells may ultimately prove to be more suitable for dermis reconstitution than currently used MSC sources [25].

A highly promising route that scientists have been researching involves HF-MSCs. A large amount of skin stem cells is located in the hair follicle bulge and are most often MSCs or EpSCs. These stem cells give rise to daughter cells that will migrate to the epidermis during wound healing and further proliferate. HF-MSCs are versatile: they can differentiate into keratinocytes, neurons, glial cells, smooth muscle cells, and melanocytes [11]. Additionally, HF-MSCs respond rapidly to skin damage by producing transient amplifying (TA) cells that facilitate acute repair. Furthermore, studies suggest that HF-MSCs demonstrate regenerative potential beyond cutaneous repair. They have the potential to support nerve repair and functional recovery of peripheral nerve and spinal cord injuries. This ability of broad tissue regeneration could give burn victims the potential of regainment of sensation post-healing [11].

EpSC therapy has also gained attention as a potential stem cell lineage to be utilized for wound treatment due to their ability to promote skin regeneration and restore essential structures of the epidermis. Traditionally, it was believed that only epidermal or hair follicle stem cells were responsible for skin regeneration following injury. However, recent evidence suggests that other sources within the skin – particularly eccrine sweat glands– may also play an active role in regeneration. Studies have shown that stem cells derived from these sweat glands (eccrine sweat gland stem cells, SGSCs) can acquire characteristics similar to those of epidermal keratinocytes when seeded in engineered dermo-epidermal substitutes. Thus, allowing them to contribute effectively to reepithelialization and long-term repair [33]. This discovery broadens the understanding of skin's regenerative potential and opens new avenues for stem cell sourcing.

Furthermore, the use of autologous epithelial stem cells offers several clinical advantages. These cells can differentiate into key skin components such as hair follicles and sweat glands, facilitating the reconstruction of more functional and natural looking tissue while minimizing scar formation.

Complications regarding immune rejection from patients are significantly reduced with the use of autologous cells. Across studies, EpSCs demonstrated faster reepithelialization and minimized scarring, while MSCs contributed more to dermal reconstruction and immune regulation [34]. Together, these findings highlight the therapeutic potential of EpSCs and SGSCs in developing advanced, patient-specific treatments for severe burn injuries.

Preclinical evidence

Preclinical studies and clinical trials experimenting with stem cell therapy for burn wounds have seen promising results (Table 1). Most often, mesenchymal stem cells are used due to their advantageous regeneration and immunoregulatory capabilities. One meta-analysis of 22 preclinical studies showed an overall improvement in burn healing rate of tissues treated with stem cells; irrespective of transplant type, burn area and treatment method of the control. Two of the studies focused on second-degree burns, 16 studies focused on third-degree burns, and the remaining 4 did not include burn degree data. Stem cell types varied from MSCs, epidermal stem cells, (ESCs), hair follicle-derived MSCs (HF-MSCs), and adipose-derived MSCs (ASCs). All except for three studies reported cell dosage, and counts varied from $0.5\text{--}21 \times 10^6$, and included limited specification on specific administration methods [35]. Hair follicle stem cells were reported to outperform other stem cell lineages with rapid proliferation and generation of a stratified epidermis, in addition to accelerated wound closure and repair when compared to the control [36]. However, it is important to note that MSCs, ESCs and ASCs all outperformed the control groups in their respective studies. Additionally, MSCs were the most abundantly used stem cell type ($n=11$) which could lead to inaccurate efficacy comparisons. The analyzed studies also suggest that stem cell therapy seems to exert greater benefit to those with second-degree burns in comparison to first or third-degree, however this finding may reflect bias due to limited sample size ($n=2$ for second-degree burns). Another note was that autologous stem cells did not provide a significantly better therapeutic effect than allogeneic or xenogeneic stem cells [35]. While this meta-analysis provides valuable insight into early preclinical trials, the amount of variation between studies makes interpreting results difficult to navigate. A systematic review of preclinical studies done by Lukomskyj et al. reinforced the notion that MSCs are the most common and effective stem cells used in current studies, with promising wound healing acceleration [6].

Amini-Nik and colleagues conducted a preclinical study using isolated MSCs from the dermal component of discarded burned skin. Isolated cells were expanded in vitro and formatted into biomaterial sheets to then be applied to full thickness burn excisional wounds of subjects. Results showed faster wound healing and closure in the group treated with burn-derived MSCs (BD-MSCs). The utilization of injured skin that is considered “waste tissue” otherwise is groundbreaking for stem cell research in relation to burn victims. The ability to isolate viable stem cells from this tissue is extremely advantageous in patients with high surface area burns, who would otherwise have very limited un-injured area to obtain skin grafts from. As the cells belong to the patient, the risk of immunological reaction and rejection is low. Additionally, cell isolation from the burned skin is a non-invasive method considering the removal of burned skin is part of routine medical practice [25]. Wound healing was evaluated by granulation tissue formation and the state of cell proliferation. Both of which showed pro-wound healing properties of BD-MSCs when compared to the control consistent with accelerated wound healing and a significant reduction in scarring. The study

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concluded no adverse side effects and no tumorigenic potential in vitro or in vivo. However, it is worth noting that assessment of tumorigenesis was only evaluated for a short period (20 days).

Inflammatory responses in acute burn healing have been proven to be harmful due to downstream systemic effects. Systemic inflammation is a major concern with severe burn victims, as it is deadly if left uncontrolled. One systematic review of eight preclinical studies concluded that MSC treatment of burns decreased tissue inflammation and damage. MSCs introduced to burn wounds have been shown to reduce serum levels of pro-inflammatory cytokines, improve renal function by reduced cell apoptosis, inhibit tissue damage, and improve overall patient survival rates. Furthermore, MSCs have proven to reverse burn-induced pathological damage in the BBB, decreasing the likelihood of neurological deficits [37]. Additionally, a meta-analysis of five studies showed decreased levels of Interleukin-1 (IL-1) and sufficient inhibition of TNF- α in burn wounds treated with MSCs compared to the controls [38-42], suggesting MSCs to have immunomodulatory capabilities advantageous to severe burn treatment.

Another potential avenue regarding EpSCs are epithelial stem cell-derived exosomes (EpSC-Exos). These organelles have been observed to promote skin regeneration for severe burn patients. In one study involving thirty rats with full-thickness skin defects, EpSC-Exos were tested for their ability to enhance wound healing and modulate cellular activity within the damaged tissue. The exosomes were injected around the wound site once per week for four weeks. The results demonstrated that specific microRNAs contained within the EpSC-Exos facilitated advanced wound healing by preventing fibroblasts from differentiating into myofibroblasts through the inhibition of TGF- β 1 expression [43]. Myofibroblasts are often associated with excessive scarring in severe burns. These findings suggest that EpSC-Exos not only promote faster and more effective tissue regeneration but also reduce scar formation. Additionally, the concentration of proteins CD31+ and nestin+ in the EpSC-Exos group were higher than the control group indicating promotion of vessel and nerve regeneration, respectively. Duan and colleagues state that EpSC-Exo resilience against degradation during systemic circulation makes them potentially more efficient and safer than their parental cells—EPSCs [43]. However, further studies are required to prove this hypothesis.

Clinical evidence

Due to the novelty of stem cell treatment for severe burns, human model trials are limited. Most recent trials investigating the topic are still in progress or have yet to report findings [44, 45] However, one phase I/II clinical trial examined the safety and efficacy of allogeneic BD-MSC transplantation in human patients with second-degree burns. The results showed that patients responded well to treatment with 100% wound closure and minimal evidence of fibrosis. Findings also suggested that multiple treatment doses were not statistically significant for accelerated healing [46]. With these findings, it can be argued that the prevalence of clinical trials analyzing MSC and EpSC treatment for burns must be expanded to address the current gaps in research.

Author/year	Article type	Model (species, burn type)	Cell type/source	Delivery method	Dosage	Outcomes	Notable findings/limitations	Adverse effects
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Li et al. (2020)	Meta-analysis (n=22 preclinical studies).	Rats (n=14), mice (n=6), minipigs (n=2). Second-degree burns (n=2), third degree burns (n=16), unknown (n=4).	MSCs (n=11), ESCs (n=2), HF-MSCs (n=1), ASCs (n=6), SVF (n=2). Xenogenic (n=9), allogeneic (n=9), autologous (n=5).	Intravenous injection (n=1), subcutaneous injection (n=19), unknown (n=2).	0.5-21 x 10 ⁶ . Unknown (n=3).	Improved burn healing rate in stem cell treatment group irrespective of transplant type, burn area, and treatment method in the control group.	Notable findings: HF-MSCs exerted the most beneficial effects. Second-degree burn wounds observed more benefits compared to third-degree. Limitations: inconsistent methods between studies.	None reported.
Lukomskyj et al. (2020)	Systemic review (n=33 preclinical studies).	Rats (n=17), mice (n=13), porcine (n=3). Second-degree (n=6), third-degree (n=23), unspecified (n=4).	MSCs. Xenogenic (n=18), allogeneic (n=1), autologous (n=14).	Scaffolds, type varies between studies.	N/A not reported.	Stem cell treatment groups showed advanced healing overall.	Notable findings: Increased proliferation and accelerated wound closure, reduced inflammation, increased vascularization, increased collagen production. Limitations: inconsistent methods between studies, cell dosages not reported.	Inflammation, ulceration, fibrosis but no mortality (n=2). Mild to moderate hemorrhaging (n=1).
Amini-Nik et al. (2018)	Preclinical study.	Rats (n=10), Yorkshire pigs	BD-MSCs. Xenogen	BD-MSCs embedded in Matrigel	N/A, not reported.	Stem cell treatment groups showed advanced	Notable findings: Stem cell treatment	None reported.

		(n=4).	eic.	(rats). BD-MSC seeded meshed bilayer Integra® (pigs).		healing overall.	groups displayed accelerated wound healing, thinner keratinocyt e layers, and reduced scar formation compared to the control.	
Eldaly et al. (2022)	System ic review (n=8 prelini cal studies)	Rats (n=6), mice (n=2). Third- degree burns.	BM- MSCs (n=3), UC-MSCs (n=3), UC-MSC- Exo (n=2). Xenogen eic (n=4), allogenei c (n=4).	Intramus cular injection (n=1), intraven ous injection (n=5), subcutan eous injection (n=1), intrader mal injection (n=1).	5×10^5 - 5×10^6 . 800 µg UCMSC- exosome s IV (n=2).	MSC groups showed decrease in pro- inflammatory markers, fewer apoptotic cells, and improved survival rates.	Notable findings: UC-MSCs showed reversal of all burn induced changes in the BBB. Limitations: high variability in methods.	None reported.
Duan et al. (2021)	Prelini cal study.	Rats (n=30). Full- thickness skin defect.	EpSC- Exos. Xenogen eic.	Initially: EpSC- Exos dissolved into HydroMa trix and was used as a scaffold. Subsequ ently: subcutan eous injection (200 µl) of EpSC- Exos	5×10^4 .	EpSC-Exo treatment group showed improved wound healing when compared to the control.	Notable findings: EpSC-Exo treatment group had increased wound healing rate and suppressed scar formation, regeneratio n of skin appendages and more organized collagen deposition,	None reported.

				dissolved into PBS and hydrogel.			nerve and vessel regeneration, inhibition of inflammatory markers.	
Schulman et al. (2022).	Phase I/II clinical trial.	Humans. Deep second-degree burns.	BM-MSCs. Allogeneic.	Two-dose escalation protocol. Topical or by injection under transparent film dressing.	2.5×10^3 BM-MSC/cm ² (n=5), 5×10^3 BM-MSC/cm ² (n=5).	BM-MSC group had 100% wound closure and minimal evidence of fibrosis.	Notable findings: The difference in healing rates between the two groups was not statistically significant.	None reported.
NTC026198 51	Phase II clinical trial, completed. Controlled, parallel, open-label trial.	Humans. Deep second-degree burns.	ASCs. Allogeneic.	N/A, trial data incomplete.	N/A, trial data incomplete.	N/A, trial data incomplete.	N/A, trial data incomplete.	N/A, trial data incomplete.
NTC053445 21	Phase 1 clinical trial, not yet recruiting. Single-blind, randomized.	Humans. Full-thickness burns.	BD-MSCs. Autologous.	BD-MSCs combined with Integra®.	5,000-20,000 cells/cm ² .	N/A, trial incomplete.	N/A, trial incomplete.	N/A, trial incomplete.

Table 1: Summary of analyzed preclinical and clinical data.

Advantages and Limitations

The use of stem cells in severe burn treatment carries both advantages and limitations. For instance, MSCs have demonstrated the ability to accelerate wound healing by enhancing reepithelialization, stimulating granulation tissue formation, and promoting more organized collagen deposition during healing. They also contribute to angiogenesis by noticeably improving vascularization within the wound bed, as well as contributing to the immune response by helping to regulate excessive inflammation. Furthermore, EpSC therapy shows potential to not only minimize fibrosis, but also improve the overall quality of healed skin by potentially restoring glands, nerves, and hair follicles. These capabilities are advantageous to patients due to reducing the risk of chronic wounds and hypertrophic scarring. MSCs can be derived from multiple sources including bone marrow, adipose tissue, umbilical cord tissue, and even the patient's own burned epithelia. EpSCs are also widely available and can be derived from hair follicle bulges, umbilical cord lining, and the mucous membranes of the oral cavity [47]. Additionally, the efficacy of stem cell treatment appears not to be constrained by wound size. Consistent results show that regardless of the size of the burned area, treatment is effective [48]. The flexibility seen in MSCs and EpSCs is highly promising to the scientific community as it allows for clinical versatility and more advanced care than what is currently marketed.

Several challenges remain for clinicians to overcome before stem cell treatment can be considered a first line treatment option. Protocols are not yet standardized, and cell sourcing, dosage, and delivery methods are all still fluid within preclinical studies and clinical trials. Most of the supporting evidence comes from animal studies due to the lack of large-scale human trials. This limitation leads to a restricted ability to confirm treatment safety and efficacy long term. Additionally, both MSC and EpSC survival rates are often low in the hostile environment of inflamed burn tissue suggesting the need for preconditioning or biomaterial encapsulation. Furthermore, potential safety risks such as immunological reactions or tumorigenicity have not been fully resolved. Long-term assessment of treatment groups post-treatment is required for safety to be thoroughly evaluated. Practical barriers including the cost and complexity of cell harvesting, culture, and storage hinder widespread study and use. Lastly, stem cells have not yet been shown to outperform or replace established treatments such as grafting, which suggests their role is currently best considered as an adjunctive rather than a primary treatment option.

Future directions

Future research in stem cell-based burn therapy for severe burns is focused on regenerating skin that is not only structurally healed, but also functionally complete. By re-establishing functional skin, patients will be able to maintain homeostatic conditions much easier than patients left with severe scar tissues seen in current burn patients. While regenerative medicine will inherently increase healing time, it will primarily focus on restoring lost glands, hair follicles, nerve endings and dermal vasculature. Both MSCs and EpSCs demonstrate regenerative potential based on emerging evidence. Some research further suggests that combining multiple types of stem cells, such as epithelial and mesenchymal cells, may have synergistic effects. Further investigation into the co-administration of MSCs and EpSCs is needed as these could improve both structural reconstruction and immune regulation [11].

Significant challenges including scientific hurdles, ethical issues, and lack of protocol standardization

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remain to be resolved before stem cell therapy can be integrated into clinical practice. Particularly, determining optimal cell administration and dosage needs to be determined through more research and experimentation [11]. The comparative benefits of local versus systemic administration in burn patients has not yet been established, and identifying the optimal approach will further the implementation of standard protocols for stem cell treatment in severe burn victims. An increase in clinical trials is needed to fully grasp the regenerative capabilities of stem cell therapy. Protocol regulation and fluidity among trials is also a critical factor currently missing among data that needs to be addressed.

Advances in supportive technologies such as biomaterial scaffolds, 3D bioprinting, and preconditioning or gene-editing of stem cells may further enhance therapeutic efficiency and viability within the hostile microenvironment of burn tissue. As these innovations mature, stem cell therapy has the potential to evolve from an experimental adjunct to a clinically integrated component of comprehensive burn care.

Summary and Conclusions

Severe burn injuries remain one of the most challenging conditions to treat in modern medicine, as they are associated with high morbidity and mortality, long recovery times, and lasting impairment of both function and appearance. Standard approaches such as excision, grafting, and advanced dressings are effective in promoting wound closure and have become more efficient with modern technologies. However, they do not address the regeneration of functioning skin or prevent excessive scarring. In recent years, stem cells have emerged as a promising therapeutic option due to their ability to control inflammation, stimulate angiogenesis, promote fibroblast activity, and enhance reepithelialization. Literature reviewed in this paper highlights consistent evidence from preclinical studies and one phase I/II clinical trial that stem cells can improve granulation tissue formation, accelerate healing, reduce scarring, and contribute to the regrowth of functional skin.

Despite these promising results, the movement of stem cell therapy into routine clinical use for severe burn victims remains limited. Most data come from preclinical animal models. Current studies are small-scale and short-term, lacking standardized protocols for cell sourcing, dose, or delivery. The long-term safety and efficacy of stem cell interventions have yet to be explored. Issues such as cell viability in the harsh burn environment, potential immunological complications, and the optimal timing for administration require further investigation. Ethical concerns and tight regulations on stem cells also continue to constrain clinical progress.

Future research should prioritize large-scale clinical trials to confirm efficacy and safety in human patients. Assessing optimal delivery strategies such as biomaterial scaffolds, hydrogels, or engineered skin substitutes is needed. Combining stem cells with other regenerative tools—growth factors, extracellular vesicles, other stem cell types—may also enhance therapeutic outcomes. While the current evidence base behind stem cell therapy is not advanced enough to replace current standards of care, further research could enable its evolution to become the center of regenerative treatment for severe burns and chronic wounds.

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